organic solvent, there is a consensus that some water is absolutely needed for the catalytic function of the enzyme.[18] We have investigated abzyme 21H3's water requirements in our octane assay medium (Figure 1B). In order to take full advantage of the immunoglobulin's optimal rates of reaction (using 0.6 mg of antibody), a water concentration of approximately 15% (v/v) was needed. *Nevertheless, excellent catalytic activity was still observed as low as 2% (v/v) water addition, and abzyme activity could still be detected in 0.12% (v/v) water.* Finally, it is interesting to note the hyperbolic curve obtained in figure 1B. From this plot it is reasonable to infer that water is affecting the kinetics by specific interactions with the catalytic antibody. In this case water acted as an activator; hence, a saturation curve was observed.

An investigation of catalytic antibodies in aqueous–organic biphasic and low water content media was undertaken. Hopefully, the experimental results garnered in this study will be conducive to further exploration of catalytic antibodies in organic solvents.[19]

Acknowledgment. This research was supported in part by a grant from the National Science Foundation (9116377).

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Synthesis of Carbocyclic Analogues of Guanosine 5′-(β-L-Fucopyranosyl diphosphate) (GDP-Fucose) as Potential Inhibitors of Fucosyltransferases

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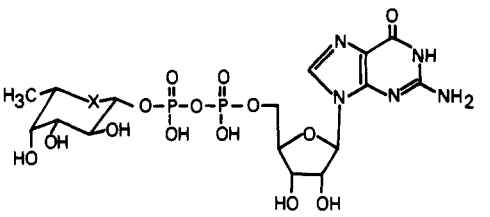
Received September 21, 1992

Summary: Two carbocyclic analogues of GDP-fucose consisting of 5a-carba-β-L-fucopyranose and its unsaturated counterpart have been synthesized as potential inhibitors of fucosyltransferases through the intramolecular Emmons–Horner–Wadsworth olefination of the 2,6-dioxophosphonate derivative, readily available from L-fucose, followed by chemo- and stereoselective reductions of the α,β-unsaturated inosose intermediate, which are the critical steps.

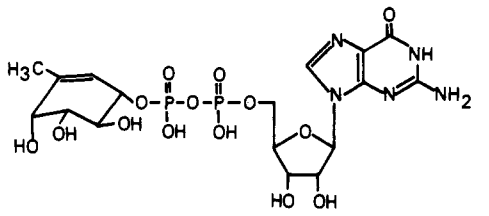
The fucosyltransferases (Fuc-T) are enzymes which catalyze transfer of L-fucopyranose from GDP-fucose (GDP-Fuc) to appropriate glycoconjugates. A number of studies have shown that invasiveness of tumor cells is correlated with an elevation of serum Fuc-T activity[1] or an increased fucose incorporation into cell surface glycoproteins.[2,3] Since fucose occurs at nonreducing termini in glycoconjugates,[4] it is conceivable that these phenomena are associated with structural changes in cell surface carbohydrates, in particular, changes involving glycoconjugate fucosylation.[5] Recently, the Lewis-type α(1→3/4)Fuc-T has gained special interest[6,7] due to its ability to synthesize

Scheme I



GDP-Fuc X = O

1 X = CH_2



2

both sialosyl Le^X [SLe^X: Neu5Acα2→3Galβ1→4-(Fucα1→3)GlcNAc] and sialosyl Le^a [SLe^a: Neu5Acα2→3Galβ1→3(Fucα1→4)GlcNAc] determinants. Both determinants have been identified as ligands for endothelial–leukocyte adhesion molecule 1 (ELAM-1)[8] and for granule membrane protein 140 (GMP-140).[9] The interaction of SLe^X/SLe^a with ELAM-1 and GMP-140 seems to play an important role in an early stage of leukocyte extravasation and the inflammatory responses.[10] Inhib-

(1) Some of the recent papers include: (a) Yazawa, S.; Madiyalakan, R.; Izawa, H.; Asao, T.; Furukawa, K.; Matta, K. L. *Cancer* **1988**, *62*, 516. (b) Yazawa, S.; Asao, T.; Nagamachi, Y.; Abbas, S. A.; Matta, K. L. *J. Cancer Res. Clin. Oncol.* **1989**, *115*, 451. (c) Asao, T. *Kitakanto Igaku* **1990**, *40*, 63; *Chem. Abstr.* **1990**, *112*, 214558t. (d) Tachikawa, T.; Yazawa, S.; Asao, T.; Shin, S.; Yanaihara, N. *Clin. Chem.* **1991**, *37*, 2081. (e) Amano, N.; Moriyama, M.; Hibi, N.; Tsukada, Y. *Rinsho Byori* **1992**, *40*, 182; *Chem. Abstr.* **1992**, *117*, 5183f.

(2) Bolscher, J. G.; Bruyneel, E. A.; Van Rooy, H.; Schallier, D. C. C.; Mareel, M. M. K.; Smets, L. A. *Clin. Expl. Metastasis* **1989**, *7*, 557.

(3) It has been suggested that the antineoplastic activity of 6-thioguanine, a clinically useful drug for the treatment of the acute leukemias, might be due to the inhibition of fucose incorporation into cellular glycoproteins by suppressing GDP-Fuc biosynthesis. See: Lazo, J. S.; Hwang, K. M.; Sartorelli, A. C. *Cancer Res.* **1977**, *37*, 4250.

(4) Flowers, H. M. *Adv. Carbohydr. Chem. Biochem.* **1981**, *39*, 279 and references cited therein.

(5) (a) A review: Smets, L. A.; Van Beek, W. P. *Biochim. Biophys. Acta* **1984**, *738*, 237. (b) Schwartz, R.; Schirrmacher, V.; Muehlradt, P. F. *Int. J. Cancer* **1984**, *33*, 503. (c) Ripka, J.; Shin, S. I.; Stanley, P. *Mol. Cello. Biol.* **1986**, *6*, 1268.

(6) See minireviews: (a) Brandley, B. K.; Swiedler, S. J.; Robbins, P. W. *Cell* **1990**, *63*, 861. (b) Macher, B. A.; Holmes, E. H.; Swiedler, S. J.; Stults, C. L. M.; Srnka, C. A. *Glycobiology* **1991**, *1*, 557.

(7) Berg, E. L.; Robinson, M. K.; Mansson, O.; Butcher, E. C.; Magnani, J. L. *J. Biol. Chem.* **1991**, *266*, 14869.

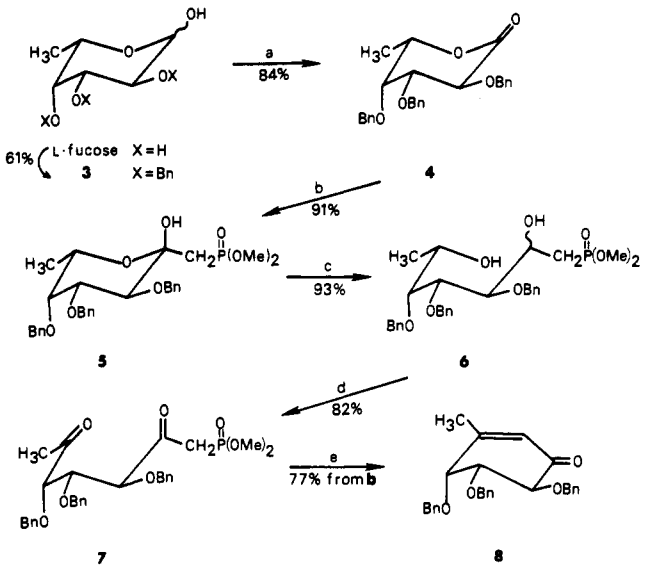
(8) (a) Phillips, M. L.; Nudelman, E.; Gaeta, F. C. A.; Perez, M.; Singhal, A. K.; Hakomori, S.; Paulson, J. C. *Science* **1990**, *250*, 1130. (b) Walz, G.; Aruffo, A.; Kolanus, W.; Bevilacqua, M.; Seed, B. *Science* **1990**, *250*, 1132.

(9) (a) Polley, M. J.; Phillips, M. L.; Wayner, E.; Nudelman, E.; Singhal A. K.; Hakomori, S.; Paulson, J. C. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 6224. (b) Handa, K.; Nudelman, E. D.; Stroud, M. R.; Shiozawa, T.; Hakomori, S. *Biochem. Biophys. Res. Commun.* **1991**, *181*, 1223.

(10) (a) Stoolman, L. M. *Cell* **1989**, *56*, 907. (b) Osborn, L. *Cell* **1990**, *62*, 3.

0022-3263/92/1957-6693$03.00/0

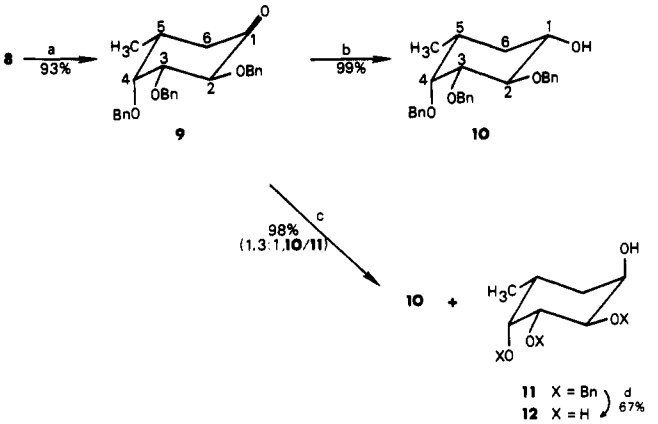
Scheme II[a]



[a] Key: (a) DMSO, Ac_2O, rt, overnight; (b) $LiCH_2P(O)(OMe)_2$, THF, N_2, −77 °C, 30 min; (c) $NaBH_4$, THF, rt, overnight; (d) DMSO, TFAA, Et_3N, CH_2Cl_2, −77 °C, 1.5 h; (e) NaH, diglyme, N_2, 65 °C, 1 h.

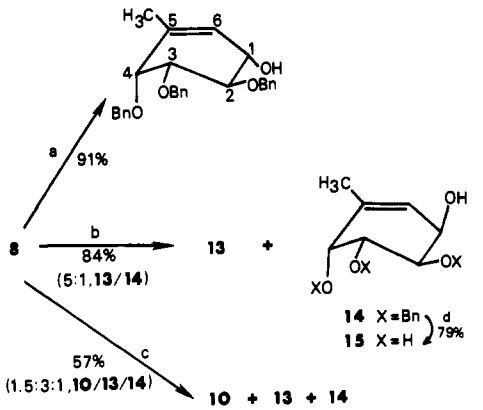
itors of Fuc-T have, therefore, potential medical applications as antimetastatic and antiinflammatory agents. Our approach[11] to the construction of such inhibitors is based on the replacement of the glycosyl moiety of sugar nucleotide donors by a more stable carba-sugar (pseudo-sugar).[12] In this paper, we report enantiospecific and expeditious synthesis of novel carbocyclic analogues of GDP-Fuc, 1 and 2, as potential inhibitors of Fuc-T[13]

Scheme III[a]



[a] Key: (a) $(Ph_3PCuH)_6$, H_2O, THF, N_2, rt, 48 h; (b) $NaBH_4$, $CeCl_3$, MeOH, rt, 5 min; (c) $NaBH_4$, EtOH, rt, 4 h; (d) 10% Pd/C, H_2 (1 atm), EtOH, rt, overnight.

Scheme IV[a]



[a] Key: (a) $NaBH_4$, $CeCl_3$, MeOH, rt, 5 min; (b) 9-BBN, THF, N_2, 0 °C for 2 h and rt for 1 h; (c) $NaBH_4$, MeOH/THF, −20 °C, 1 h; (d) Li, liquid NH_3, THF, 2 h.

(Scheme I).

The conversion of L-fucose to its carbocyclic analogues was achieved by a straightforward route involving intramolecular Emmons–Horner–Wadsworth olefination[14,15] of the 2,6-dioxo phosphonate 7, which proceeded with retention of the stereogenic centers at C-2, C-3, and C-4 in L-fucopyranose (Scheme II). The synthesis of 7 started from the known hemiacetal[16] 3, readily accessible from L-fucose in three steps[17] (61% yield). Albright–Goldman oxidation[18] of 3 to the 1,5-lactone 4,[19] followed by a nucleophilic substitution reaction with the carbanion derived from dimethyl methylphosphonate, afforded the heptulopyranose 5 as a single anomeric isomer.[20] Reductive ring

(11) The efforts in developing inhibitors for glycosyltransferases have been concentrated on the production of the structural analogues of donors and acceptors. Some of the recent examples include: (a) Nucleotide analogues: Hatanaka, K.; Slama, J. T.; Elbein, A. D. *Biochem. Biophys. Res. Commun.* **1991**, *175*, 668. (b) Sugar nucleotide/nucleoside analogues: Camarasa, M. L.; Fernandez-Resa, P.; Garcia-Lopez, M. T.; De las Heras, F. G.; Mendez-Castrillon, P. P.; Alarcon, B.; Carrasco, L. *J. Med. Chem.* **1985**, *28*, 40. Kijima-Suda, I.; Toyoshima, S.; Itoh, M.; Furuhata, K.; Ogura, H.; Osawa, T. *Chem. Pharm. Bull.* **1985**, *33*, 730. Kijima-Suda, I.; Miyamoto, Y.; Toyoshima, S.; Itoh, M.; Osawa, T. *Cancer Res.* **1986**, *46*, 858. Prehm, P. Ger. Offen. DE 3428976, 1986; *Chem. Abstr.* **1987**, *107*, 40267b. Vaghefi, M. M.; Bernacki, R. J.; Dalley, N. K.; Wilson, B. E.; Robins, R. K. *J. Med. Chem.* **1987**, *30*, 1383. Vaghefi, M. M.; Bernacki, R. J.; Hennen, W. J.; Robins, R. K. *J. Med. Chem.* **1987**, *30*, 1391. Orbe, M.; Claesson, A. *Eur. J. Med. Chem.* **1989**, *24*, 447. Ikeda, K.; Nagao, Y.; Achiwa, K.; *Carbohydr. Res.* **1992**, *224*, 123. (c) Carbohydrate acceptor analogues: Kuan, S. F.; Byrd, J. C.; Basbaum, C.; Kim, Y. S. *J. Biol. Chem.* **1989**, *264*, 19271. Hecker, S. J.; Minich, M. L.; Lackey, K. *J. Org. Chem.* **1990**, *55*, 4904. Hindsgal, O.; Kaur, K. J.; Srivastava, G.; Blaszczyk-Thurin, M.; Crawley, S. C.; Heerze, L. D.; Palcic, M. M. *J. Biol. Chem.* **1991**, *266*, 17858. (d) Peptide acceptor analogues: Bause, E.; *Biochem. Soc. Trans.* **1983**, *11*, 105. (e) Bisubstrate analogues: Palcic, M. M.; Heerze, L. D.; Srivastave, O. P.; Hindsgaul, O. *J. Biol. Chem.* **1989**, *264*, 17174.

(12) The term "pseudo-sugar" was originally proposed by McCasland et al. to name a class of compounds in which the ring-oxygen atom of a sugar pyranose was replaced by a methylene group: McCasland, G. E.; Furuta, S.; Durham, L. J. *J. Org. Chem.* **1966**, *31*, 1516. Recently, Suami and Ogawa recommend the use of the prefix "carba" preceded by the appropriate locant ("4a" for an aldofuranose or "5a" for an aldopyranose) instead of "pseudo" for an indexing purpose. See their review article on carba-sugar (pseudo-sugar) chemistry: Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21.

(13) Some of the compounds have been reported to inhibit the activity of Fuc-T. See: (a) Guanine nucleotides: Bella, A., Jr.; Kim, Y. S. *Biochem. J.* **1971**, *125*, 1157; *Arch. Biochem. Biophys.* **1971**, *147*, 753. Holmes, E. H. *J. Biol. Chem.* **1990**, *265*, 13150. (b) *N*-Ethylmaleimide: Chou, T. H.; Murphy, C.; Kessel, D. *Biochem. Biophys. Res. Commun.* **1977**, *74*, 1001. (c) Heparin: Jork, R.; Loessner, B. *Biomed. Biochim. Acta* **1985**, *44*, 537. (d) Cytosolic protein: Martin, A.; Ruggiero-Lopez, D.; Biol, M. C.; Louisot, P. *Biochem. Biophys. Res. Commun.* **1990**, *166*, 1024. (e) Substrate analogues: see the papers by Hindsgaul et al. in ref 11c and by Palcic et al. in ref 11e.

(14) The intramolecular olefination has been employed to transform carbohydrates into the corresponding carba-sugars and their derivatives; see: (a) Paulsen, H.; Von Deyn, W. *Liebigs Ann. Chem.* **1987**, 125. (b) Marquez, V. E.; Lim, M.-I.; Tseng, C. K.-H.; Markovac, A.; Priest, M. A.; Khan, M. S.; Kaskar, B. *J. Org. Chem.* **1988**, *53*, 5709. (c) Fukase, H.; Horii, S. *J. Org. Chem.* **1992**, *57*, 3651.

(15) For a review on cycloalkane formation by intramolecular Wittig reaction, see: Becker, K. B. *Tetrahedron* **1980**, *36*, 1717.

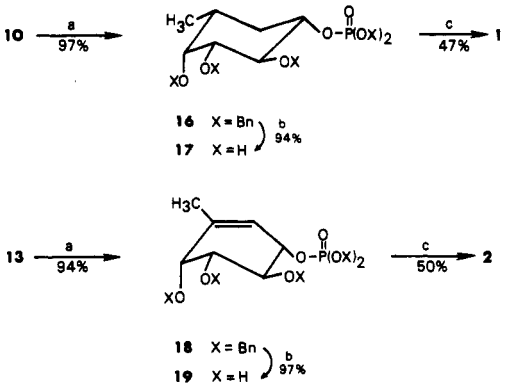
(16) Dejter-Juszynski, M.; Flowers, H. M. *Carbohydr. Res.* **1971**, *18*, 219.

(17) For the preparation of the first intermediate, methyl α-L-fucopyranoside, see: Zehavi, U.; Sharon, N. *J. Org. Chem.* **1972**, *37*, 2141.

(18) Albright, J. D.; Goldman, L. *J. Am. Chem. Soc.* **1965**, *87*, 4214; **1967**, *89*, 2416.

(19) All new compounds, except the unstable dioxophosphonate 7, were fully characterized on the basis of their ^1H NMR spectra and MS analyses (see supplementary material).

Scheme V[a]



[a] Key: (a) (1) $(BnO)_2PN(i\text{-}Pr)_2$, 1*H*-tetrazole, CH_2Cl_2, rt, 2 h and (2) *m*-CPBA, −40 °C → 0 °C, 45 min; (b) Li, liquid NH_3, THF, 2 h; (c) (1) Dowex 50X8-400 (Et_3HN^+), (2) GMP-morpholidate, pyridine, rt, 5 d, (3) HPLC (RP-18; 24:1 0.05 M aq Et_3HNHCO_3–MeCN, isocratic), and (4) Bio-Rad AG 50W-X2 (Na^+).

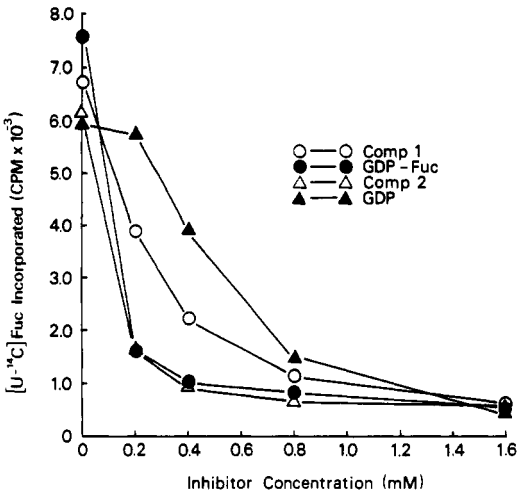


Figure 1. Effect of carbocyclic analogues of GDP-Fuc, 1 and 2, on α(1→3/4)Fuc-T activity.

opening of **5** with $NaBH_4$ to the heptitol **6** and subsequent Swern oxidation[21] yielded the unstable dioxo phosphonate **7**. The ensuing intramolecular olefination of **7** occurred smoothly by treatment with NaH in diglyme[22] to give the unsaturated inosose **8** ($[\alpha]_D$ −105°, *c* 1.0, $CHCl_3$) in 94% yield. The use of K_2CO_3 as base in the presence of 18-crown-6[14b,c] afforded the product in a lower yield (≈60%).

The copper(I) hydride hexamer $(Ph_3PCuH)_6$[23] allowed the stereoselective conjugate reduction of **8** yielding the desired inosose **9** ($J_{H\text{-}5,H\text{-}6ax}$ = 13.8 Hz) as the only detectable diastereoisomer in 93% yield (Scheme III). Apparently, the hydride was delivered to the less-hindered side of **8**. The $NaBH_4$–$CeCl_3$ reduction in MeOH[24] furnished an almost quantitative conversion of **9** to the equatorial alcohol **10** ($J_{H\text{-}1,H\text{-}2}$ = 9.3 Hz), which was the suitably protected carba-β-L-fucopyranose required for the subsequent phosphorylation. In the absence of $CeCl_3$ the same reduction resulted in a poor stereoselectivity giving a mixture of **10** and its epimeric alcohol **11** ($J_{H\text{-}1,H\text{-}2}$ = 2.4 Hz) in a ratio of 1.3:1. Hydrogenolysis of **11** yielded 5a-carba-α-L-fucopyranose[25] (**12**) (mp 142–143 °C; $[\alpha]_D$ −81°, *c* 1.0, H_2O).

Stereoselective 1,2-reduction of the carbonyl moiety in **8** was successful by treatment with $NaBH_4$–$CeCl_3$ in MeOH,[24] which afforded exclusively the desired pseudoequatorial alcohol **13** ($\delta_{H\text{-}6}$ 5.47, $J_{H\text{-}1,H\text{-}6}$ = 1.2 Hz)[26] in 91% yield (Scheme IV). However, the reduction with $NaBH_4$ alone produced a mixture of diastereoisomers **13** and **14** ($\delta_{H\text{-}6}$ 5.53, $J_{H\text{-}1,H\text{-}6}$ = 4.3 Hz)[26] together with the saturated alcohol **10** in a ratio of 3:1:1.5. The 1,2-reduction was effected also with 9-BBN in THF,[27] but with less satisfactory results, producing a 5:1 mixture of **13** and **14**. The Birch reduction[28] of **14** afforded the unsaturated analogue of carba-α-L-fucopyranose **15** ($[\alpha]_D$ −272°, *c* 1.0, H_2O).

Phosphorylation of **10** and **13** proceeded smoothly in high yields by phosphitylation using dibenzyl *N,N*-diisopropylphosphoramidite and 1*H*-tetrazole, followed by oxidation with *m*-CPBA[29] (Scheme V). Subsequent Birch reduction[28] of the resulting perbenzylated phosphates **16** and **18** yielded carba-β-L-fucopyranosyl phosphate (**17**) ($[\alpha]_D$ −1.6°, *c* 1.0, H_2O) and its unsaturated analogue **19** ($[\alpha]_D$ −55°, *c* 0.7, H_2O), respectively, in excellent yields. The phosphates **17** and **19** were then coupled to GMP-morpholidate according to a standard procedure[30] to give our target compounds **1** ($[\alpha]_D$ −14.0°, *c* 1.0, H_2O) and **2** ($[\alpha]_D$ −19.9°, *c* 0.7, H_2O), respectively.

Preliminary inhibition assay[31] was carried out against α(1→3/4)Fuc-T solubilized from human colonic adenocarcinoma Colo205 cells using lacto-*N*-fucopentaose 1 (LNF 1: Fucα1→2Galβ1→3GlcNAcβ1→3Galβ1→4Glc) as a substrate[32] (Figure 1). Both carbocyclic analogues **1** and **2** exhibit a potent inhibitory activity more strongly than GDP.[13a] Furthermore, the activity of **2** is comparable to that of GDP-Fuc. The half-chair conformation of the cyclohexene ring in **2** could probably mimic the Fuc-T transition state by adopting, albeit not perfectly, the flattened anomeric conformation of the fucosyl intermediate.

Detailed biological characterization of these novel inhibitors will be the subject of a forthcoming paper.

Acknowledgment. We thank Robert Goldberg for carrying out the synthesis of GDP-Fuc and M.E. Salyan for FABMS analyses, both at this institute. This work was supported by funds from The Biomembrane Institute.

(20) The ^1H NMR spectrum indicated **5** to exist in a single anomer. Although the anomeric configuration has not been determined yet, one can assume that the nucleophile approached from the less-hindered side of the carbonyl group to form an axially disposed hydroxyl group, i.e., an α-anomer. See also ref 14c.

(21) Huang, S. L.; Omura, K.; Swern D. *Synthesis* **1978**, 297.

(22) Grieco, P. A.; Pogonowski, C. S. *Synthesis* **1973**, 425.

(23) (a) Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1989**, *30*, 5677. (b) Koenig, T. M.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron Lett.* **1990**, *31*, 3237.

(24) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(25) Very recently, 5a-carba-α-L-fucopyranose has been synthesized by radical cyclisation of 7-deoxy-7-ido-D-*manno*-hept-1-enitol derivatives and reported to have mp 115 °C and $[\alpha]_D$ −58° (c 1, MeOH). See: Redlich, H.; Sudau, W.; Szardening, A. K.; Vollerthun, R. *Carbohydr. Res.* **1992**, *226*, 57.

(26) On the basis of the ^1H NMR studies on the antiobiotic valienamine, 1D-(1,3,6/2)-6-amino-4-(hydroxymethyl)-4-cyclohexene-1,2,3-triol, and its derivatives, it is reported that a vicinal pseudoequatorial substituent (i.e., 1-OH in **13**) causes the resonance of an olefinic proton (H-6) to move upfield relative to the pseudoaxial epimer (i.e., **14**): Toyokuni, T.; Ogawa, S.; Suami, T. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1161.

(27) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1975**, *40*, 1864.

(28) McCloskey, C. M. *Adv. Carbohydr. Chem.* **1957**, *12*, 137.

(29) Yum, K.-L.; Fraser-Reid, B. *Tetrahedron Lett.* **1988**, *29*, 979.

(30) (a) Nunez, H. A.; O'Connor, J. V.; Rosevear, P. R.; Baker, R. *Can. J. Chem.* **1981**, *59*, 2086. (b) Gokhale, U. B.; Hindsgaul, O.; Palcic, M. M. *Can. J. Chem.* **1990**, *68*, 1063. (c) Schmidt, R. R.; Wegmann, B.; Jung, K.-H. *Liebigs Ann. Chem.* **1991**, 121.

(31) For the methods of enzyme preparation and inhibition assay, see supplementary material.

(32) This enzyme catalyzes the transfer of L-fucose from GDP-Fuc to the 4-OH of the GlcNAc residue in LNF 1 yielding Le^b-hexasaccharide [Fucα1→2Galβ1→3(Fucα1→4)GlcNAcβ1→3Galβ1→4Glc]. See also ref 6b.

Supplementary Material Available: Experimental procedures, including the methods of enzyme preparation and inhibition assay, and ^1H NMR spectra for all new compounds, except for the unstable dioxophosphonate 7 (24 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Articles

Synthesis of the Hydroxyethylene Isostere of Leu-Val

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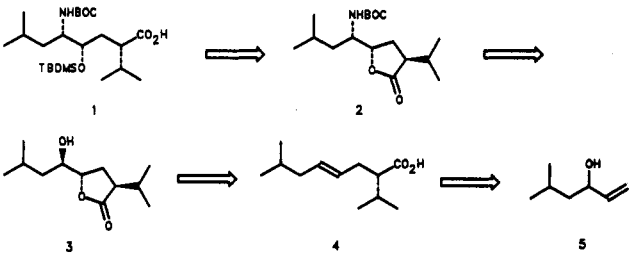
The hydroxyethylene isostere of the dipeptide leu-val was synthesized from isovaleryl aldehyde in nine steps in 15% overall yield without the use of chromatographic separations. A key finding is the ability of an amide to selectively direct an epoxidation in an acyclic system and that the selectivity is a function of the amide's size.

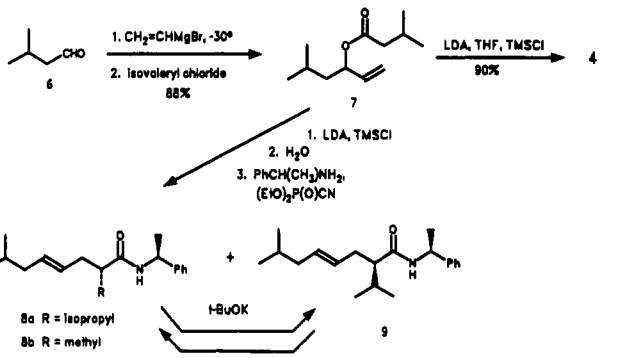
The dipeptide hydroxyethylene isostere of leu-val 1 is a representative of an important class of unnatural amino acids related to the natural amino acid statine that when incorporated into peptide substrates of proteolytic enzymes such as Renin impart pronounced inhibitory effects. The inhibitory action is believed to occur by mimicking the transition state for amide hydrolysis. More recently, the same strategy has been used to develop inhibitors of a key protease of the human immunodeficiency virus (HIV).[1]

Earlier, we described a synthesis of 1 utilizing leucine as a starting material and source of chirality.[2,3] We would now like to describe a new more economical approach that promises to be much more general, does not require a single chromatographic purification, does not pass through sensitive intermediates, and can easily be scaled up for commercial development. The strategic concept of the synthesis is outlined in Scheme I. The success of this approach lies in the ability to prepare the acid 4 with a stereogenic center at C-2 and to transfer that chirality to the centers at C-4 and C-5. Although a number of approaches for the preparation of acid 4 are readily envisioned, we chose to use the Ireland enolate Claisen rearrangement[4] for both economic reasons and its known ability to transfer chirality present in the allylic alcohol precursors.[5] The required ester 7 (Scheme II) is prepared in 88% distilled yield by the slow addition of 3-methylbutyraldehyde (6) to a slurry of vinylmagnesium bromide

Scheme I



Scheme II



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